PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 January 2001 (09.01.01)	
International application No. PCT/GB00/01788	**Applicant's or agent's file reference** WARM / P22403PC
International filing date (day/month/year) 10 May 2000 (10.05.00)	**Priority date** (day/month/year) 10 May 1999 (10.05.99)
Applicant BRYANS, Justin, Stephen et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 November 2000 (30.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Jean-Marc Vivet
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
WARM / P22403PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 01788	10/05/2000	10/05/1999
Applicant		
WARNER-LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/36 C07D295/13 C07D215/46 A61K31/167 A61K31/445
A61K31/47 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EDWARD F. ELSLAGER ET AL.: "Respiratory Drugs. VIII. Ester and Amide Congeners of Amodiaquine, Hydroxychloroquine, Oxychloroquine, Primaquine, Quinacrine and Related Substances as Potential Long-Acting Antimalarial agents" JOURNAL OF MEDICINAL CHEMISTRY., vol. 12, no. 4, July 1969 (1969-07), pages 600-607, XP002145190 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 cited in the application page 603, column 1, 3rd paragraph and compound XIIIa	1-4
A	US 5 654 301 A (HAROLD L. KOHN ET AL.) 5 August 1997 (1997-08-05) claims; examples	1,25-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 13336 A (RESEARCH CORPORATION TECHNOLOGIES) 2 April 1998 (1998-04-02) claims; examples	1,25-28
A	WO 98 50343 A (SMITHKLINE BEECHAM) 12 November 1998 (1998-11-12) claims; examples	1,25-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5654301 A	05-08-1997	US 5378729 A	03-01-1995
		AU 657985 B	30-03-1995
		DE 69223965 D	12-02-1998
		DE 69223965 T	30-04-1998
		EP 0592490 A	20-04-1994
		JP 6510985 T	08-12-1994
		AT 161824 T	15-01-1998
		AU 2162192 A	08-01-1993
		CA 2110693 A	10-12-1992
		WO 9221648 A	10-12-1992
		AU 641160 B	16-09-1993
		AU 5519590 A	28-02-1991
		CA 2017217 A	19-11-1990
		EP 0400440 A	05-12-1990
		JP 3506045 T	26-12-1991
		NZ 233728 A	28-04-1993
		PT 94103 A,B	08-01-1991
		WO 9015069 A	13-12-1990
		AT 92315 T	15-08-1993
		DE 3786865 A	09-09-1993
		DE 3786865 T	09-12-1993
		DK 526087 A	08-04-1988
		EP 0263506 A	13-04-1988
		ES 2005042 A	16-02-1989
		ES 2058085 T	01-11-1994
		GR 871549 A	12-02-1988
		IE 61437 B	02-11-1994
		JP 2580196 B	12-02-1997
		JP 63132832 A	04-06-1988
		NZ 222045 A	27-10-1989
		PT 85869 A,B	01-11-1987
		AT 62222 T	15-04-1991
		AU 596573 B	10-05-1990
		AU 5371186 A	21-08-1986
		DE 3678469 D	08-05-1991
		DK 72686 A	16-08-1986
		EP 0194464 A	17-09-1986
		ES 552348 D	16-10-1987
		ES 8708142 A	01-12-1987
		GR 860455 A	18-06-1986
		IE 58422 B	22-09-1993
		JP 1972065 C	27-09-1995
		JP 6104649 B	21-12-1994
		JP 61200950 A	05-09-1986
		PT 82032 A,B	01-03-1986
WO 9813336 A	02-04-1998	US 5880158 A	09-03-1999
WO 9850343 A	12-11-1998	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PFIM/P22403PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01788	10/05/2000	10/05/1999
International Patent Classification (IPC) or national classification and IPC C07C233/36		
Applicant WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/11/2000	07.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Slootweg, A Telephone No. +49 89 2399 8326

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01788

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-21	as originally filed				

Claims, No.:

1-29	as received on	15/06/2001	with letter of	14/06/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 27-29.

because:

☒ the said international application, or the said claims Nos. See Separate Sheet. relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. For the assessment of the present claims 26-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Claims 26-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:

D1	=	EDWARD F. ELSLAGER ET AL.: 'Repository Drugs. VIII., J. Med. Chem., vol. 12, no. 4, July 1969 (1969-07), pages 600-607, cited in the application,
D2	=	US-A-3 118 941,
D3	=	LARIZZA, ANGELO ET AL.: Gazz. Chim. Ital., vol 90, 1960, p. 848- 862,
D4	=	MÖHRLE ET AL.: Arch. Pharm., no. 316, 1983, p.251-256,
D5	=	MÖHRLE ET AL.: Arch. Pharm., no. 303, 1970, p.531-544,
D6	=	MÖHRLE ET AL.: Arch. Pharm., no.316, 1983, P. 222-229,
D7	=	SCHWARTZ ET AL.: Tett. Lett., vol. 23, no. 9, 1982, p. 979-82,
D8	=	MÖHRLE ET AL.: Tetrahedron, vol 26,, 1970, p. 4895-4900,
D9	=	Compound with CAS reg. nr 92493-02-2 (Beilstein extract)
D10	=	WO-A-98/50343

D11 = WO-A-98/13336
D12 = US-A-5 654 301

The documents D2-D9 were not cited in the international search report. Copies of the documents are appended hereto.

3. The document D1 discloses on p.603 the compounds XIIIa and XIIIb stating that this is useful as an antimalarial repository drug.

4. The document D3 discloses at the bottom of p. 849 the compound Ph-CH_2-NR-CHR_1CH_2-R_2 with definitions given for R, R_1 and R_2 (compounds are defines as being anti-histaminic). See also the compounds in Table II on p. 852 the compounds 201 FC and 198 FC.

5. Documents D2, D4-D9 also disclose compounds which have been disclaimed from claim 1 but no medical use is indicated for any of the compounds disclosed. The medical use claim is therefore formulated to include these compounds.

6. The closest prior art documents are considered to be the documents D10-D12 which disclose different amide compounds for use in the treatment of CNS disorders (D10), specifically as anti convulsant (D11-D12).

7. The problem to be solved by the present application can be see to provide alternative compounds which can be used in the treatment of CNS disorders.

8. The solution to this problem is the compounds as claimed in claim 1 (the compounds which were disclosed in D1-D9 have been excluded by means of a disclaimer). As such claim 1 can be considered to satisfy Art. 33 (2) PCT, with respect to the cited prior art.

9. There is no indication in the prior art documents which could have led the skilled man to make such compounds to treat CNS disorders. The documents D1 and D3 do show a medical use but not the use to treat CNS disorders. Claim 1 can, therefore, also be considered to satisfy Art. 33 (3) PCT, with respect to the cited prior art.

10. Claims 2-24 are dependent on claim 1 and as such can also be considered to satisfy Art. 33 (2) and (3) PCT for the same reasons.

11. Claim 25 is a claim towards pharmaceutical compositions of compounds according to claim 1 including the compounds disclosed in D2, and D4-D9 (which did not exhibit any medical use), but excluding the compounds disclosed in D1 and D3 (which did exhibit a medical use). Claim 26 is a claim towards the medical use of the compounds defined in claim 25. Claims 25 and 26 can, therefore, also be considered to satisfy Art. 33 (2) and (3) PCT, with respect to the cited prior art.

Re Item VII

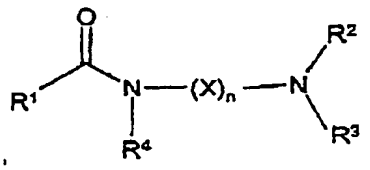
Certain defects in the international application

12. The citation given on p. 1, l. 26-28 of the description obviously contains an error since this document could not be retrieved.

13. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D12 is not mentioned in the description, nor are these documents identified therein.

What is claimed is:

1. A compound of formula I



wherein :

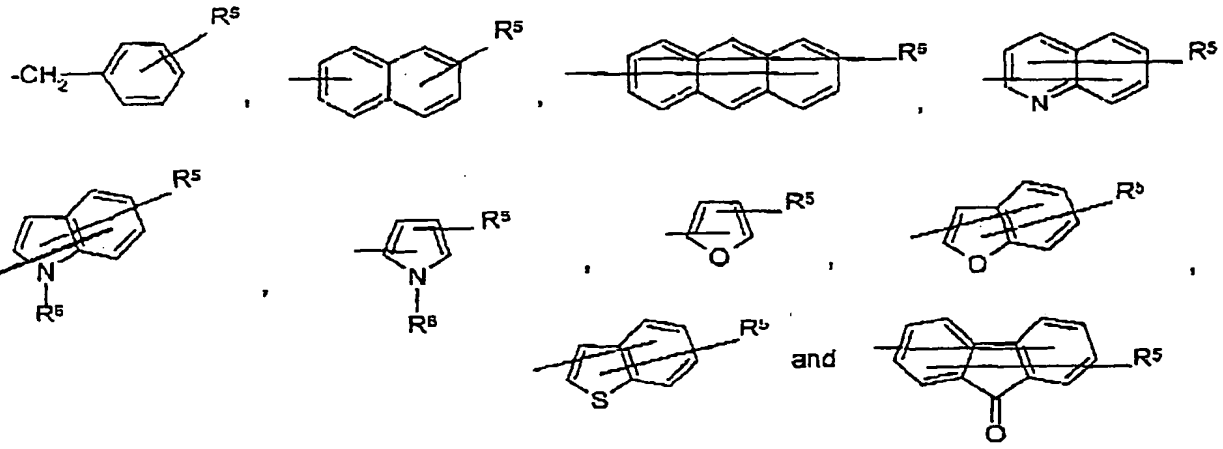
R^1 is hydrogen, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

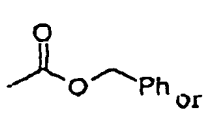
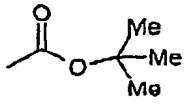
R^2 and R^3 independently are hydrogen, C_1-C_4 alkyl, phenyl or benzyl, or taken together with the nitrogen to which they are attached complete a ring having from 4 to 7 ring atoms, one optionally being oxygen;

X is $(CH_2)_n$, $CHMe\text{-}(CH_2)_{n-1}$ or $(CH_2)_{n-1}\text{-}CHMe$,

n is 1, 2 or 3;

R^4 is an aromatic or heteroaromatic group selected from



wherein R^5 is hydrogen, halogen, C_1-C_4 alkyl, nitro, N_3 or CF_3 and R^6 is hydrogen, C_{1-4} alkyl, -(C=O)Me, -(C=O)NH_2,  or  ;

and the pharmaceutically acceptable salts thereof

with the proviso that in formula I:

when R^1 is CH_3, $(X)_n$ is $(CH_2)_3$, and R^2 and R^3 are both ethyl, R^4 is not 7-chloroisoquinol-4-yl;

when R^1 is H, $(X)_n$ is $(CH_2)_2$ and R^2 and R^3 are both ethyl, R^4 is not benzyl, 4-methylbenzyl, 4-chlorobenzyl, 2-chlorobenzyl, 4-bromobenzyl, 3-ethylbenzyl, 4-isopropylbenzyl, 4-n-propylbenzyl, 3-n-butylbenzyl, 2-t-butylbenzyl, 4-s-butylbenzyl or 2-bromobenzyl;

when R^1 is methyl or ethyl, $(X)_n$ is $CHMeCH_2$ and NR^2R^3 is N-piperidinyl, R^4 is not benzyl;

when R^1 is H, $(X)_n$ is CH_2 and R^4 is benzyl, NR^2R^3 is not $NHCH_2Ph$, N-piperidinyl, NH-t-butyl, N-morpholinyl, N-pyrrolidinyl, N-azepinyl, $N(CH_3)_2$ or $N(CH_2CH_3)_2$; and

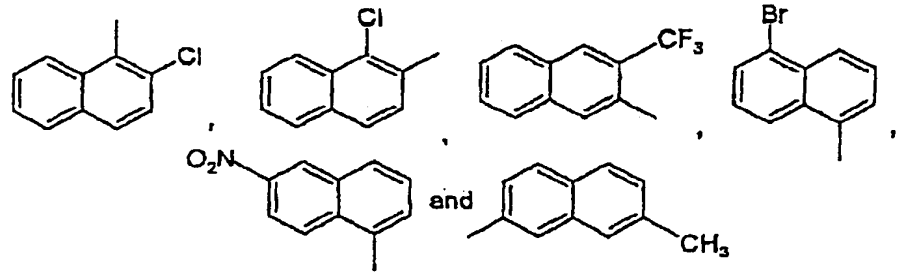
when R^1 is n-butyl, $(X)_n$ is $(CH_2)_2$ and R^4 is benzyl, NR^2R^3 is not $NHCH_2Ph$

2. A compound according to claim 1 wherein R^1 is C_1-C_4 alkyl.

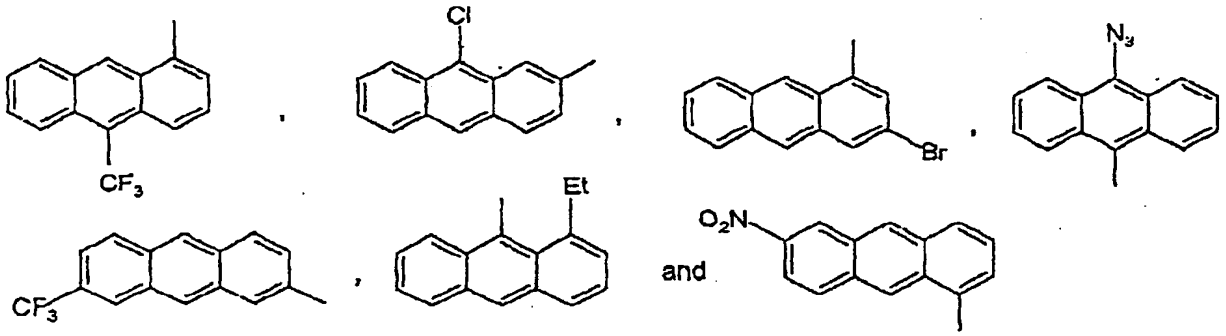
3. A compound according to Claim 2 wherein R^2 and R^3 independently are C_1-C_4 alkyl.

4. A compound according to Claim 3 wherein n is 2 or 3.

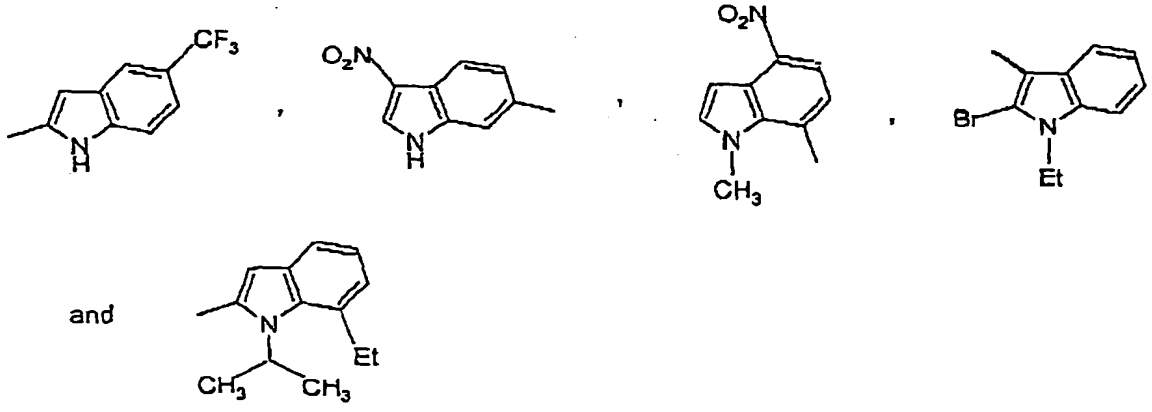
5. A compound according to Claim 4 wherein R^4 is selected from



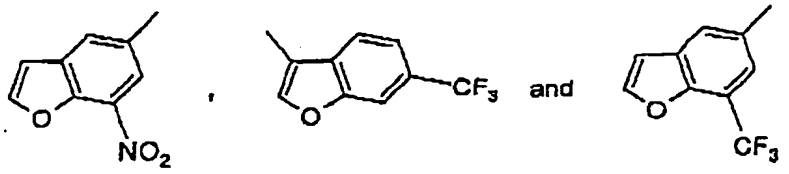
6. A compound according to Claim 4 wherein R^4 is selected from



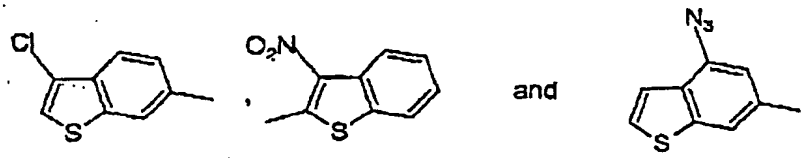
7. A compound according to Claim 4 wherein R^4 is selected from



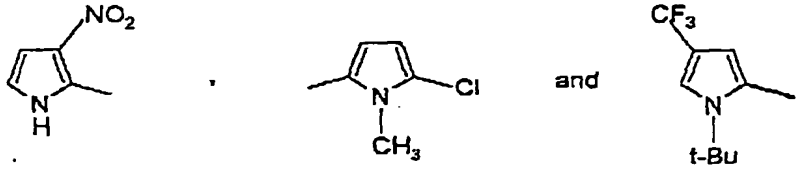
8. A compound according to Claim 4 wherein R^4 is selected from



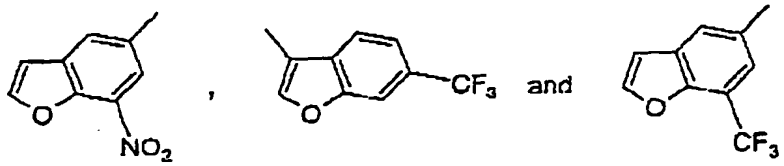
9. A compound according to Claim 4 wherein R^4 is selected from



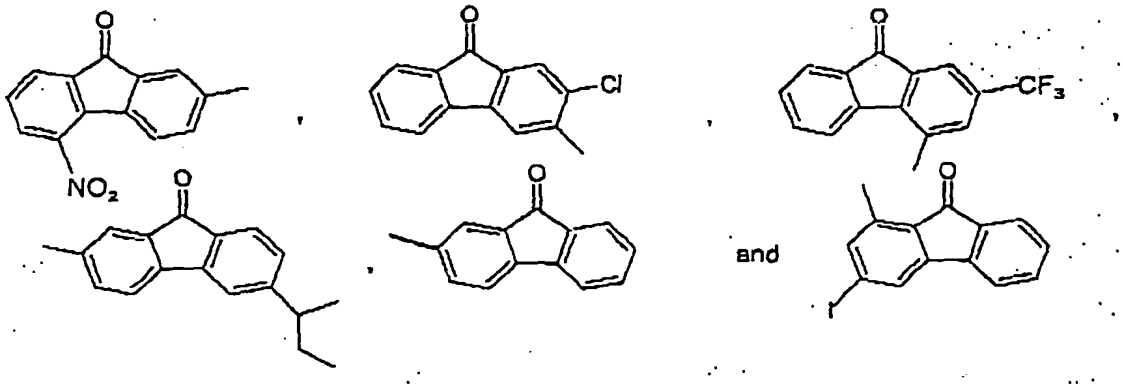
10. A compound according to Claim 4 wherein R^4 is selected from



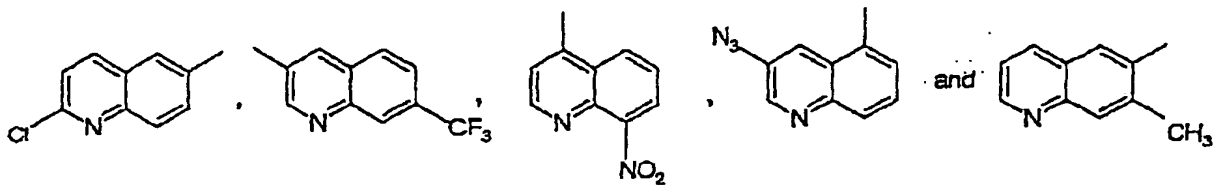
11. A compound according to Claim 4 wherein R^4 is selected from



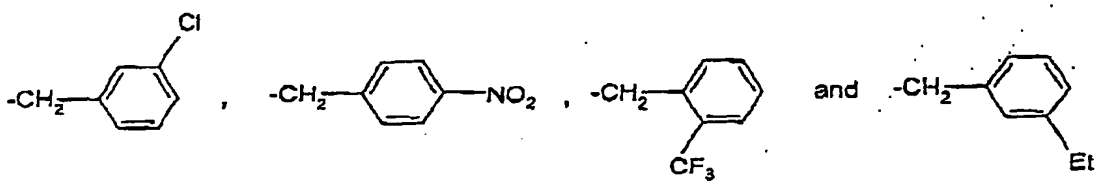
12. A compound according to Claim 4 wherein R^4 is selected from



13. A compound according to Claim 4 wherein R^4 is selected from



14. A compound according to Claim 4 wherein R^4 is selected from



15. A compound according to any one of Claims 5 to 14 which is selected from

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone

N-Propionyl, N-(2-Diethylaminoethyl)- 1-amino-4-bromonaphthalene

N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2- (3-diethylamino-propyl))-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzyl-amine

N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine

N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene

N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide

N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene, and

N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

16. N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene.

17. N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone.

18. N-Propionyl, N-(2-diethylaminoethyl)- 1-amino-4-bromonaphthalene.

19. N-Propionyl, N-(N-morpholino)-1-amino-4-chloronaphthalene.

20. N-Propionyl, N-(2-(3-diethylamino-propyl))-1-amino-4-chloronaphthalene.

21. N-Propionyl, N-(2-diethylaminoethyl)-1-amino-4-azidonaphthalene.

22. N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene.

23. N-Propionyl, N-(2-diethylaminoethyl)-(1-amino-4-nitronaphthalene).

24. A compound according to any one of Claims 1 to 23 which is a pharmaceutically acceptable salt.

25. A pharmaceutical formulation comprising a compound of any one of Claims 1 to 24 as defined in formula I without the proviso in Claim 1, provided that:
when R^1 is CH_3, $(X)_n$ is $(CH_2)_3$ and R^2 and R^3 are both ethyl, R^4 is not 7-chloroisoquinol-4-yl; and
when R^1 is methyl or ethyl, $(X)_n$ is $CHMeCH_2$ and NR^2R^3 is N-piperidinyl, R^4 is not benzyl.

26. Compound as defined in Claim 25 for use in medicine.

27. A method for treating a CNS disorder in a mammal in need of treatment comprising administering a CNS effective amount of

compound of formula I as defined in any one of Claims 1 to 24 without the proviso in Claim 1.

28. A method according to Claim 27 wherein the CNS disorder is selected from pain, depression, anxiety, or schizophrenia.

29. A method according to Claim 27 wherein the CNS disorder is selected from Huntington's disease, Alzheimer's disease or amyotrophic lateral sclerosis.

[redacted]

Express Mail No. ET401306226US

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07C 233/36, C07D 295/13, 215/46, A61K 31/167, 31/445, 31/47, A61P 25/28 — A1

(11) International Publication Number: WO 00/68184

(43) International Publication Date: 16 November 2000 (16.11.00)

(21) International Application Number: PCT/GB00/01788

(22) International Filing Date: 10 May 2000 (10.05.00)

(30) Priority Data:
60/133,359 10 May 1999 (10.05.99) US

(71) Applicant (*for all designated States except US*): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

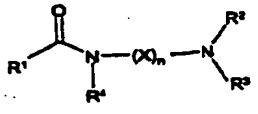
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balsham CB1 6DZ (GB). O'TOOLE, John, Colm [GB/GB]; 51 Fincham's Close, Linton, Cambridge CB1 6ND (GB). HORWELL, David, Christopher [GB/GB]; 8 West Hill Road, Foxton, Cambridge CB2 6SZ (GB).

(74) Agent: BASSETT, Richard, S.; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(81) Designated States: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AROMATIC AMIDES



(I)

(57) Abstract

Aromatic and heteroaromatic amides of formula (I) where R^1, R^2 and R^3 can be alkyl, X is alkylene, and R^4 is an unsubstituted or substituted aromatic or heteroaromatic group such as naphthyl or fluorenyl, are CNS agents useful for treating pain, depression, anxiety, seizures, and schizophrenia.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

AROMATIC AMIDES

FIELD OF THE INVENTION

This invention provides aromatic amides which are useful CNS agents, especially for treating depression, pain, anxiety, schizophrenia and seizure disorders.

BACKGROUND OF THE INVENTION

Disorders of the central nervous system have become one of the most common and most debilitating diseases currently afflicting mankind. Specific disorders such as depression and schizophrenia are now known to be common afflictions, and are routinely diagnosed. These diseases result in significant losses of an individual's ability to work and to carry out normal daily activities, and in many cases require long term hospitalization or institutionalization. Only recently have new treatments, such as the selective serotonin re-uptake inhibitors for example, become available and are effective for many people. Unfortunately, such agents are not effective for all cases of depression, and indeed can lead to significant adverse reactions in some patients.

Other CNS disorders, such as chronic pain and seizure disorders, are only marginally treatable, and such treatments often are associated with unacceptably high health risks, for instance long term use of narcotic analgesics to treat chronic pain generally results in addiction to the drug being employed, the results of which can be devastating to the patient.

Accordingly, the need continues for new medicines that will effectively treat CNS disorders without imposing unacceptable liability and risk issues. I have now discovered a series of aromatic amides which can be utilized to treat these CNS disorders, and which have a very good risk-to-benefit ratio. The invention compounds are alkyl amides having an aromatic group attached to the amide nitrogen atom.

Several N-aryl alkylamides are known in the prior art. For example, Ronsisvalle *et al.* described a series of analgesic N-thienyl acetamides in Eur. J. Med. Chem. 3: 553-559, 1998.

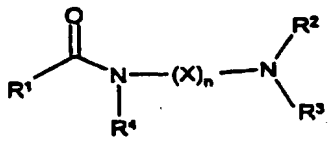
US Patent No. 4,203,988 discloses certain N-pyridyl amide derivatives as inhibitors of gastric secretion, while US No. 3,163,645 discloses N-pyridyl amides as analgesics. US No. 5,372,931 discloses N-alkoxyphenyl and N-alkoxynaphtyl amides as useful in certain analytical and diagnostic methods.

Elslager *et al.*, in J. Med. Chem. 9: 378-91, 1966, describe certain N-naphthyl amides as useful as intermediates in the synthesis of arylazo substituted naphthyl alkylenediamines. Similarly, Elslarger *et al.*, described certain N-quinolyl amides in J. Med. Chem. 12: 600-7, 1966.

The compounds provided by this invention are characterized as novel N-aryl amides having good CNS activities, and are thus useful for treating depression, anxiety, pain, schizophrenia, and seizure disorders such as epilepsy.

SUMMARY OF THE INVENTION

This invention provides N-aryl alkylamides defined by Formula I



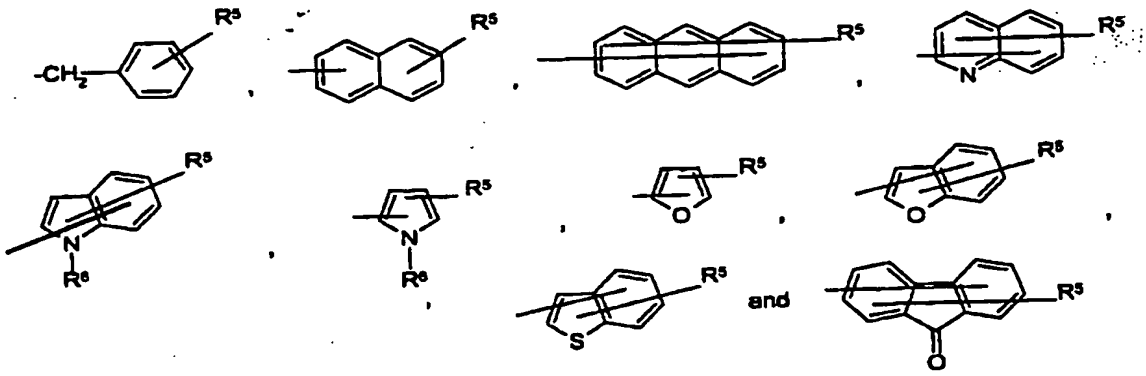
(I)

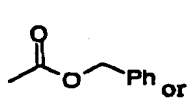
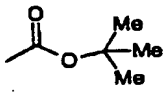
wherein :

R^1 is hydrogen, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

R^2 and R^3 independently are hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl or benzyl, or taken together with the nitrogen to which they are attached complete a ring having from 4 to 7 ring atoms, one optionally being oxygen; X is $(CH_2)_n$, CHMe-$(CH_2)_{n-1}$ or $(CH_2)_{n-1}$-CHMe, n is 1, 2 or 3;

R^4 is an aromatic or heteroaromatic group selected from



wherein R^5 is hydrogen, halogen, C_1-C_4 alkyl, nitro, N_3 or CF_3 and R^6 is hydrogen, C_{1-4} alkyl, -(C=O)Me, -(C=O)NH_2,  or  , and the pharmaceutically acceptable salts thereof.

Preferred invention compounds have Formula I wherein R^1, R^2 and R^3 independently are C_1-C_4 alkyl, and R^4 is naphthyl, substituted naphthyl, fluorene or substituted fluorene.

Also preferred are the compounds of Formula I wherein n is 2 or 3.

Another embodiment of this invention is a pharmaceutical formulation comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier, diluent or carrier therefor.

The compounds of the instant invention are useful for the treatment of CNS disorders including neurodegenerative disorders, pain, depression, convulsions, anxiety, schizophrenia and seizures.

Neurodegenerative disorders include, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia. A patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

Pain refers to acute as well as chronic pain.

Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain and allodynia.

Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive.

Still other pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache.

Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, IBS and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

The compounds of the instant invention are also expected to be useful in the treatment of anxiety, panic, schizophrenia and seizures as demonstrated by means of standard pharmacological procedures.

The invention also provides a method for treating CNS disorders in mammals, comprising administering a CNS effective amount of a compound of Formula I to a mammal in need of treatment.

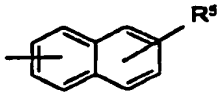
DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C_1-C_4 alkyl" means straight and branched carbon chains having from 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, *n*-butyl, *sec*-butyl and *tert*-butyl.

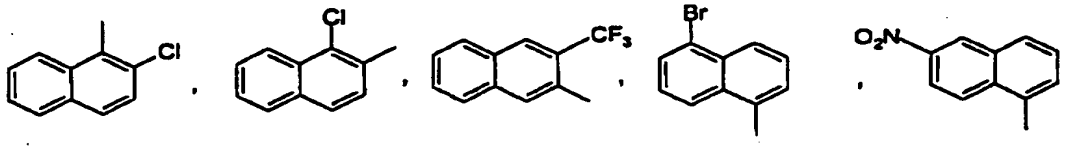
"C_2.C_4 alkenyl" means ethylene, 2-propylene and 2- or 3-butylene.

"Halo" means fluoro, chloro, bromo and iodo.

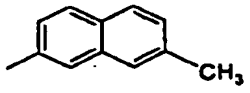
"Substituted aryl" and "substituted heteroaryl" means any of the cyclic ring systems described above having R^5 other than hydrogen, for example where R^5 is halo, C_1-C_4 alkyl, nitro or CF_3. Typical substituted aryl and substituted heteroaryl groups thus include 3-chloronaphthyl, 4-nitronaphthyl, 4-nitrobenzofuranyl, 3-methylbenzothienyl, and 1-methyl-3-trifluoromethyl indole. These are compounds of Formula I wherein R^4 is a cyclic, bicyclic or tricyclic aromatic or heteroaromatic group bearing a substituent defined as R^5, where R^5 is other than hydrogen. The group



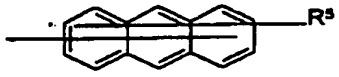
is a naphthyl ring which can be attached to the amide nitrogen (of Formula I) at any ring position. This ring can be substituted at any available ring position by the group R^5. Specific examples include :



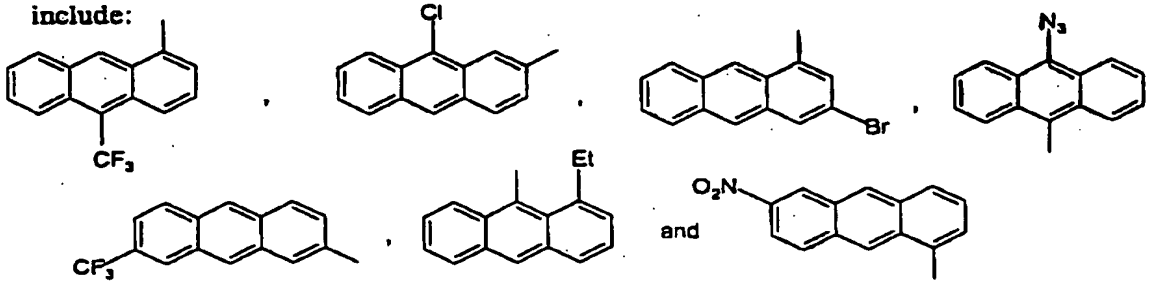
and



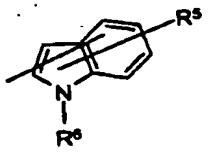
Specific examples of the group:



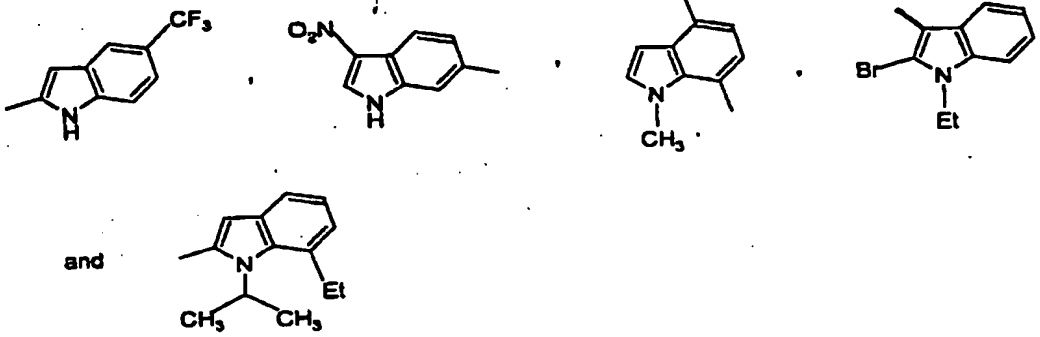
include:



Specific examples of the group:

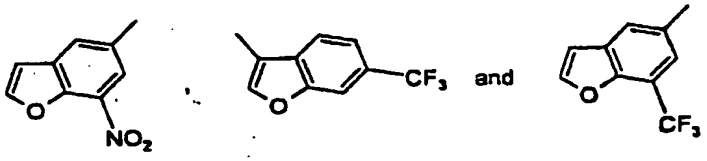


include:

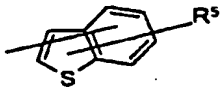


Specific examples of the group:

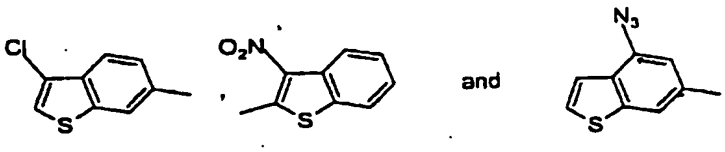
include



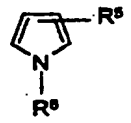
Specific examples of the group:



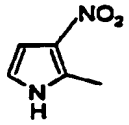
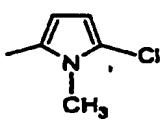
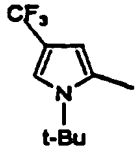
include



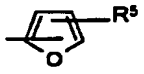
Specific examples of the group:



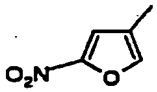
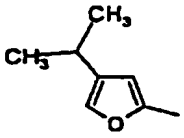
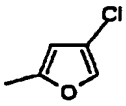
include



and


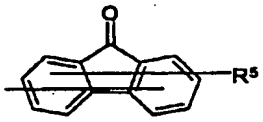
Specific examples of the group:



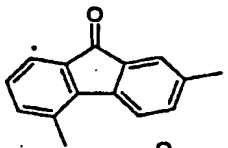
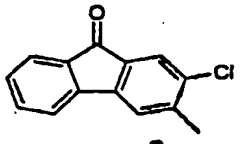
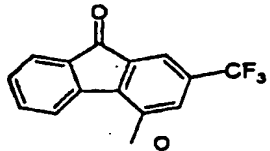
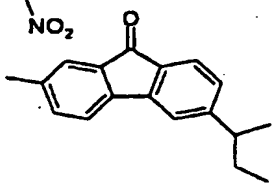
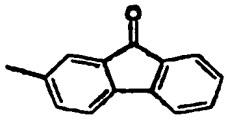
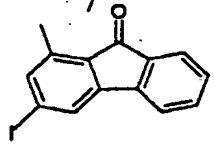
include



and


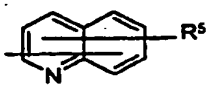
Specific examples of the group:



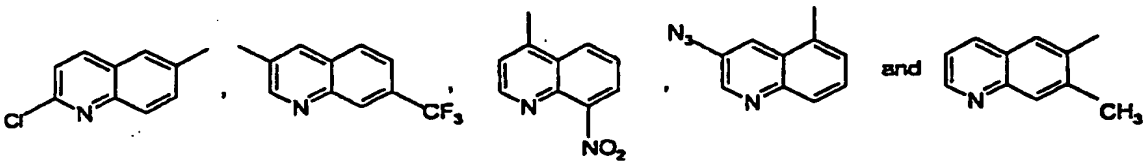
include






and


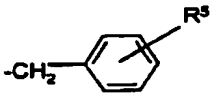
Specific examples of the group:



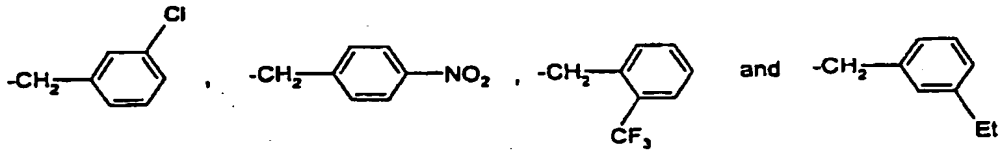
include



Specific examples of the group:



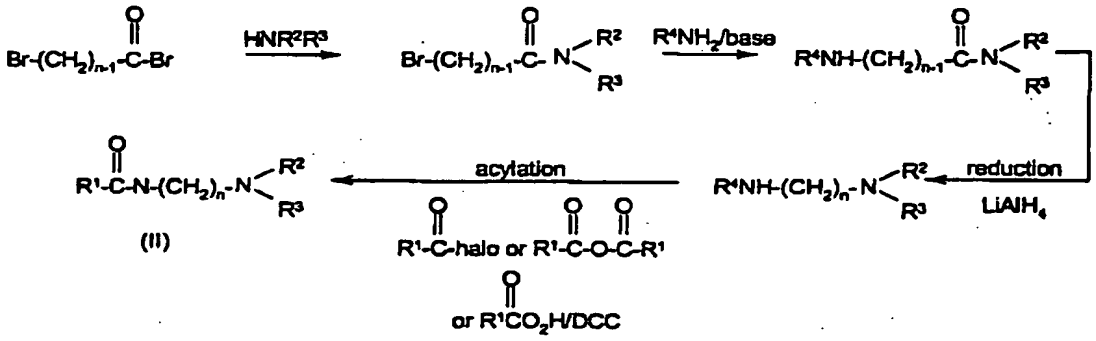
include



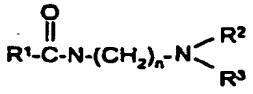
The compounds of this invention are amines and as such they readily form pharmaceutically acceptable salts by reaction with common inorganic and organic acids. Typical acids commonly used to form salts include hydrochloric, nitric, phosphoric , and sulfuric acid, as well as acetic, citric, malonic, tartaric, succinic, salicylic, methanesulfonic, oxalic and benzoic acid. Any common inorganic or organic acid can be utilized to form the pharmaceutically acceptable salts of this invention, and the specific acid to be utilized is well within the skill of the art.

The compounds provided by this invention can be prepared by any of several methods well known to those of ordinary skill in the art of organic chemistry. In a typical synthesis, an N-aryl alkyl diamine is acylated, for example by reaction with an aryl halide, or by

coupling an aryl-acid to the amide in the presence of a common peptide coupling reagent such as DCC (dicyclohexylcarbodiimide). Such synthesis can be illustrated by Scheme 1, in which an alkyl diamine is first prepared by reacting a halo substituted acyl halide with an amine HNR^2R^3, to give the corresponding halo substituted amide, reacting the halo substituted amide with an aryl amine $ArNH_2$ to give an arylaminoamide, reducing the amide carbonyl to give the corresponding arylamino alkylamine, and then acylating the arylamino nitrogen atom to give a compound of Formula II. The synthetic sequence is illustrated in scheme 1:



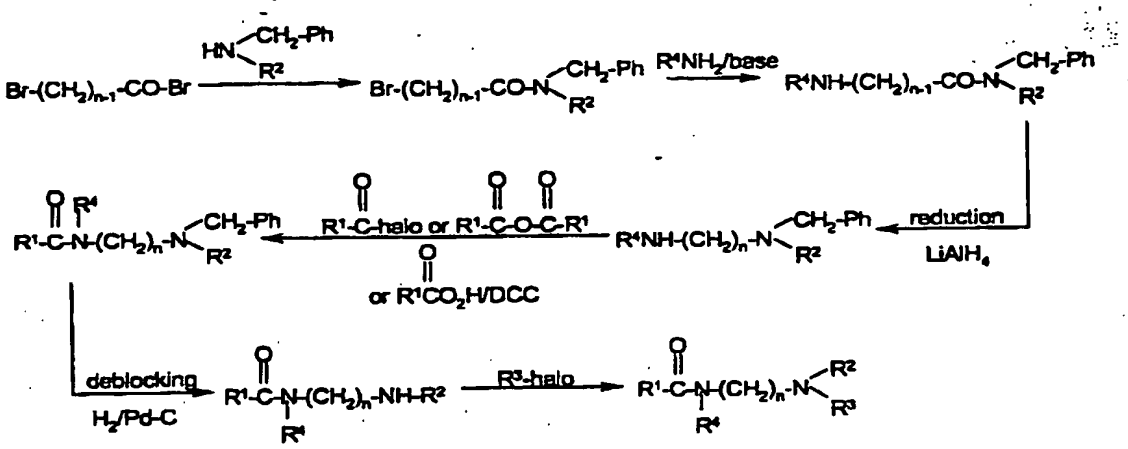
An alternative method for preparing the invention compounds comprises alkylating a terminal primary or secondary amine of the formula



(II)

where one or both of R^2 and R^3 are hydrogen, by reaction with an alkylating agent such as an alkyl halide. The reaction is depicted by scheme 2, which illustrates the synthesis of the primary or secondary amine according to the general scheme shown above, followed by a reaction with a common alkylating agent.

Scheme 2



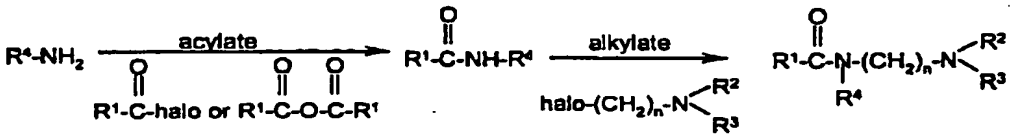
In the above scheme, the halo substituted acid halide is reacted with an amine bearing a group that is easily removed, such as benzyl. This is a normal acylation reaction that is typically carried out in a solvent such as dichloromethane or toluene, and generally is complete within 30 min to 1 h when carried out at a temperature of about 30°C to about 60 °C. The resulting amide is readily isolated by removing the solvent, and is subsequently reacted with an amine R^4NH_2 in the presence of a base such as sodium carbonate or triethylamine, and typically in a solvent such as N,N-dimethylformamide or diethyl ether. The resulting amino substituted amide is readily isolated by removing the solvent, and further purification generally is not required. The amino substituted amide is readily reduced by reaction with a reducing agent such as lithium aluminium hydride or sodium borohybride, thus affording an alkylene diamine. The alkylene diamine is coupled to an acyl group, for example by common acylation with an acid anhydride or acid halide (e.g. R^1-C(=O)-O-C(=O)-R^1 or R^1-C(=O)-halo, or by reacting the free acid R^1COOH with the amine using a coupling reagent such as dicyclohexylcarbodiimide (DCC).

The corresponding amide is next converted to a primary or secondary amine, for instance by removing a group such as benzyl by normal catalytic hydrogenation. The resulting amine is reacted with a common alkylating agent such as an alkyl halide (R^3-halo) and the

resulting product of Formula I is isolated by removing any reaction solvent and excess alkylating agent. The invention compound can be further purified if desired by routine methods such as crystallization, for example from solvents such as methanol, diethylether, ethyl acetate and the like, or chromatography over solid supports such as silica gel.

Still another way to prepare the invention compounds is to start with an aryl amine (R^4NH_2), acylate it with and acyl halide or anhydride to form an amide, and then alkylate the amide with an amino substituted alkyl halide. This process is depicted in Scheme 3 below :

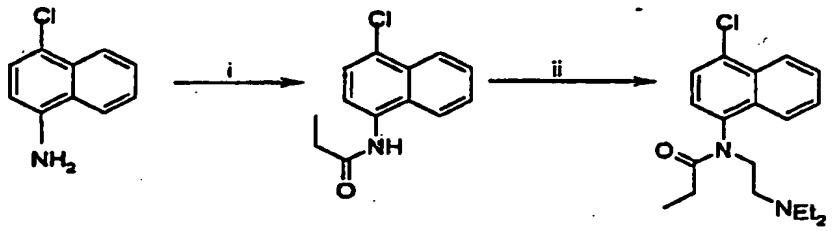
Scheme 3



These reactions are carried out under normal organic synthetic conditions. For example, an aryl amine such as 3-naphthylamine can be reacted with acetyl chloride in a solvent such as toluene. A base such as triethylamine can be utilized as an acid scavenger if desired. The reaction is substantially complete within 1 to 2 h when carried out at about 30 to 60 °C, and the product amide is readily isolated by removing the reaction solvent. The amine is then alkylated by reaction with an amino substituted amino alkyl halide to produce the invention compound of Formula I.

The synthesis of specific invention compounds is further illustrated by the following detailed example. The examples are representative only, and are not intended to limit the invention in any respect.

EXAMPLE 1



Reagents : (i) propionyl chloride, Et_3N ; (ii) NaH, $Et_2NCH_2CH_2Cl.HCl$

N-Propionyl 1-amino-4-chloronaphthalene.

To a stirred solution of 1-amino-4-chloronaphthalene (0.70 g, 3.9 mmol) in dichloromethane (50 ml) was added triethylamine (1.0 ml, 7 mmol), followed by propionyl chloride (0.5 ml, 5.8 mmol). After 20 min the mixture was diluted with ethyl acetate (150 ml) and washed with 2N HCl (100 ml) followed by saturated sodium carbonate (100 ml). The organic phase was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was triturated with a mixture of ethyl acetate and heptane, 130 ml, 3:10) to give 0.62 g (67 %) of the desired compound as a white solid.

^1H NMR 400 MHz ($CDCl_3$) : Ų 1.33 (3H, t, J = 6Hz) ; 2.56 (2H, q, J = 6Hz) ; 7.47 (1H, br s) ; 7.52-7.70, 4H, m) ; 7.84 (1H, m) ; 8.32 (1H, m).

MS ES^+: m/z 236 ($[MH]^+$, 16%), 234 ($[MH]^+$, 48%).

IR (thin film) $Ź_{max}$ (cm^{-1}) : 1652, 2922, 3300.

N-Propionyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene.

To a stirred solution of N-propionyl 1-amino-4-chloronaphthalene (400 mg, 1.7 mmol) in dry dimethylformamide (40 ml) was added sodium hydride (60% dispersion in oil, 0.2 g, 5 mmol). After 20 min, 2-diethylaminoethylchloride hydrochloride (0.4 g, 2.8 mmol) was added and the mixture stirred for a further 2 h. Water (200 ml) was added and the mixture extracted with ethyl acetate (2 x 100 ml). The organic extracts were combined, dried

($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by reverse phase chromatography (methanol:water 7:3) to give 0.27 g (47%) of the desired product as a colorless oil.

^1H NMR 400 MHz ($CDCl_3$): δ 0.97 (9H, m); 1.80 (1H, m); 2.01 (1H, m); 2.50 (4H, m); 2.69 (2H, t, J = 7Hz); 3.34 (1H, m); 4.33 (1H, m); 7.36 (1H, d, J = 8 Hz); 7.55-7.70 (3H, m); 7.84 (1H, m); 8.34 (1H, d, J = 8 Hz).

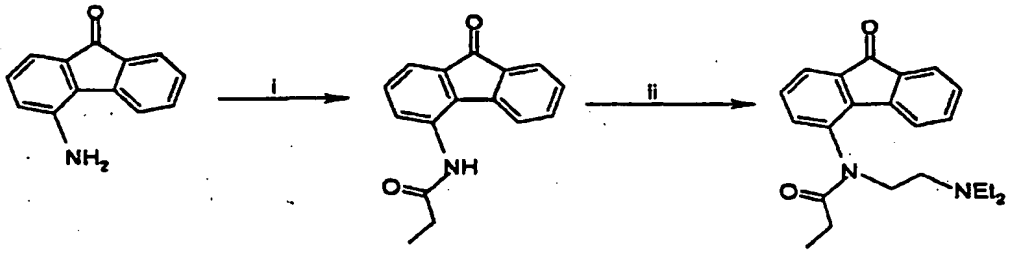
MS CI: m/z 233 ($[MH]^+$, 100 %).

IR (thin film) ν_{max} (cm^{-1}): 1667, 2970.

Microanalysis for $C_{19}H_{25}N_2OCl$

Calculated	C	68.56%	H	7.57%	N	8.42%
Found		68.29%		7.78%		8.20%

EXAMPLE 2



Reagents : (i) propionyl chloride, Et_3N ; (ii) NaH, $Et_2NCH_2CH_2Cl.HCl$

N-Propionyl 4-amino-9-fluorenone.

To a stirred solution of 4-amino-9-fluorenone (0.20 g, 1.0 mmol) in dichloromethane (40 ml) was added triethylamine (0.5 ml, 3.5 mmol), followed by propionyl chloride (0.5 ml, 5.8 mmol). After 20 min the mixture was diluted with ethyl acetate (150 ml) and washed

with 2N HCl (100 ml) followed by saturated sodium carbonate (100 ml). The organic phase was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, heptane:ethyl acetate 7:3) to give 164 mg (63%) of the desired material as a yellow oil.

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.36 (3H, br t); 2.56 (2H, br q); 7.18-7.38 (4H, m); 7.41-7.60, (2H, m); 7.71 (1H, d, J = 8 Hz); 7.83 (1H, br s).

IR (thin film) ν_{max} (cm^{-1}): 1659, 1716, 3258.

N-Propionyl, N-(2-diethylaminoethyl)-4-amino-9-fluorenone.

N-propionyl 4-amino-9-fluorenone (158 mg, 0.6 mmol) was dissolved in dry dimethylformamide (40 ml) and sodium hydride (60% dispersion in oil, 80 mg, 1.2 mmol). After 20 min, 2-diethylaminoethylchloride hydrochloride (250 mg, 1.4 mmol) was added and the mixture was heated to 80°C. After 10 min the mixture was cooled to room temperature and diluted with water (20 ml). The mixture was diluted with saturated sodium carbonate (150 ml) and the mixture extracted with ethyl acetate (2 x 70 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, dichloromethane:diethyl ether 9:1, and then 1:4) to give 0.16 g (73%) of the desired product as a colorless oil.

^{1}H NMR 400 MHz ($CDCl_3$): δ 0.95 (6H, t, J = 7 Hz); 1.05 (3H, t, J = 7 Hz); 2.08 (2H, m); 2.50 (4H, m); 2.69 (2H, m); 3.34 (1H, m); 4.34 (1H, m); 7.30-7.75 (7H, m).

MS CI : m/z 351 ($[MH]^+$, 100 %).

IR (thin film) ν_{max} (cm^{-1}): 1652, 1716, 2970.

Microanalysis for $C_{22}H_{26}N_2O_2$

Calculated	C	75.40%	H	7.48%	N	7.99%
Found		75.55%		7.57%		7.94%

EXAMPLES 3-15

By following the general procedure of Examples 1 and 2, several additional compounds of Formula I were prepared and are described in Table I below.

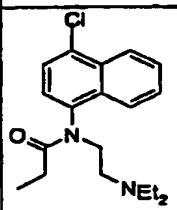
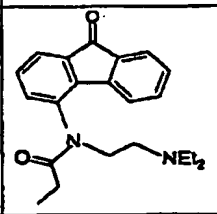
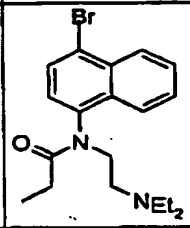
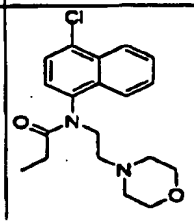
The compounds of Formula I have been evaluated in standard in vivo and in vitro assays routinely used to measure the ability of test compounds to interact with the central nervous system of animals, thereby establishing their utility for treating CNS disorders such as pain, depression, anxiety and schizophrenia. In a typical assay, compounds are evaluated for their ability to bind to the $\alpha_2\delta$ submit of the calcium channel found in animal brain tissue. Significant binding to this receptor indicates a compound's analgesic potential.

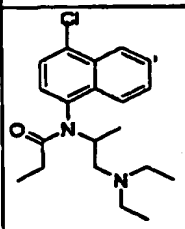
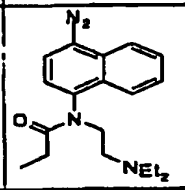
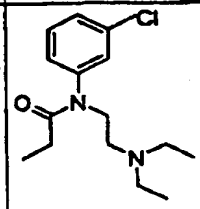
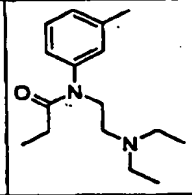
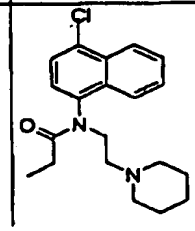
In another test, compounds were evaluated for their ability to reduce the hyperalgesia effects of carrageenin in the following assay: nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesimeter (Randall L.O. and Selitto J.J., A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn. 4: 409-419, 1957). Male Sprague-Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat Nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, 2 to 3 baseline measurements were taken before animals were administered 100 µl of 2 % aqueous carrageenin by intraplantar injection into the right hind paw.

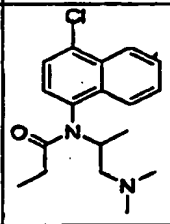
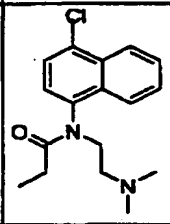
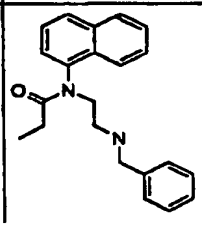
Nociceptive thresholds were taken again 3 h after carrageenin injection to establish that animals were exhibiting hyperalgesia. Animals were orally dosed with a compound of Formula I (by gavage) at 3.5 h after carrageenin injections and nociceptive thresholds were examined at 1 and at 2 h post-carrageenin.

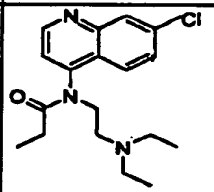
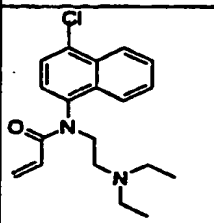
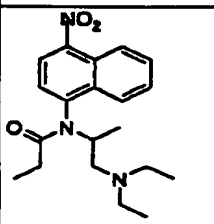
Table 1 presents the biological activity of representative invention compounds when evaluated in the above tests, and in the in vitro $\alpha_2\delta$ binding assay as described by Gee et al. in J. Biol. Chem., 1996; 271: 5776-5879, incorporated herein by reference.

Table 1

Compound	Structure	IC_{50}(μM) at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat	
			%MPE* 1h post dose @30mg/kg p.o.	%MPE* 2h post dose @30mg/kg p.o.
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene (Example 1)		0.170	51.5	22.2
N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone (Example 2)		0.058	1.1	6.4
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-bromonaphthalene (Example 3)		0.065	-2.6	7.7
N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene (Example 4)		>10	44.8	30.7

Compound	Structure	IC_{50}(μM) at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat	
			%MPE* 1h post dose @30mg/kg p.o.	%MPE* 2h post dose @30mg/kg p.o.
N-Propionyl, N-(2-(3-diethylamino-propyl))-1-amino-4-chloronaphthalene (Example 5)		5.03	23.3	27.5
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene (Example 6)		0.885	N/A	N/A
N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzylamine (Example 7)		1.7	N/A	N/A
N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine (Example 8)		4.81	N/A	N/A
N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene (Example 9)		> 10	N/A	N/A

Compound	Structure	IC_{50}(μM) at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat: %MPE* 1h post dose @30mg/kg p.o.	Carrageenin induced thermal hyperalgesia in the rat: %MPE* 2h post dose @30mg/kg p.o.
N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene (Example 10)		2.336	N/A	N/A
N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene (Example 11)		5.34	N/A	N/A
N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene (Example 12)		> 10	29.68	3.13

Compound	Structure	IC_{50}(μM) at $\alpha_2\delta$ binding site	Carrageenin induced thermal hyperalgesia in the rat %MPE* 1h post dose @30mg/kg p.o.	Carrageenin induced thermal hyperalgesia in the rat %MPE* 2h post dose @30mg/kg p.o.
N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide (Example 13)		5.47	8.6	1.2
N-Acryloyl,N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene (Example 14)		0.177	15.1	0.9
N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene (Example 15)		0.800	-5.7	2.0

*MPE: maximum possible effect – set as baseline value prior to treatment with carrageenin

As noted above, the invention compounds of Formula I are typically utilized in the form of pharmaceutical compositions for human therapy of CNS disorders. The compounds can be formulated with any excipient, diluent or carrier commonly utilized in the pharmaceutical art. Such common excipients include potato starch, corn starch, talc, sucrose, lactose, cellulose; flavoring agents such as peppermint, orange flavor and the like. Binders and lubricants such as magnesium stearate, colloidal silicon dioxide and gum tragacanth can be utilized for convenient oral or parenteral administration, for example as tablets, capsules, aqueous solutions, elixirs, syrups, and controlled release patches, pellets and suppositories, as well as solutions for IV, SC and IM injection. The formulations will typically contain from about 5 % to about 95 % of active compound of Formula I (w/w).

The preparations will be administered such that the active ingredient is presented at a dose which is effective to treat a CNS disorder. Such dose will generally be from about 0.1 to about 2000 mg/kg of body weight, typically about 1 mg to about 100 mg/kg. The formulations can be administered from 1 to about 4 times a day, or as otherwise dictated by the particular patient and condition being treated, and the attending medical practitioner.

The compounds of Formula I can additionally be utilized in combination with other active ingredients, for example selective serotonin re-uptake inhibitors such as fluoxetine hydrochloride, and any of the tricyclic antidepressants such as benzazepines and the like.

The following examples further illustrate specific formulations provided by this invention.

EXAMPLE 16

Tablets

N-Butyryl, N-(3-dimethylamino-propyl)-5-amino-indole	200 mg
Potato starch	50 mg
Magnesium stearate	25 mg
Talc	25 mg

The above ingredients are blended to uniformity and then pressed into a tablet. Such tablets are administered from 1 to 4 times a day to an adult human suffering from depression and in need of treatment.

EXAMPLE 17

Capsules

N-pivaloyl 1-amino-2-trifluoromethyl-naphthalene	300 mg
Corn starch	50 mg
Dextrose	50 mg
Magnesium oxide	1 mg

The above ingredients are blended to uniformity and filled into an empty telescoping gelatin capsule. Such capsules are administrated from 1 to 4 times a day to an adult human suffering from schizophrenia and in need of treatment.

EXAMPLE 18

Parenteral solution

N-propionyl,N-(2-diethylaminoethyl)(1-amino-4-bromonaphthalene), hydrochloride salt	500 mg
isotonic saline	qs 1000 ml

The invention compound is dissolved in 1000 ml of isotonic saline and filled into a sterile plastic bottle equipped with a drip tube. The solution is administered IV to a human suffering from chronic pain resulting from colon carcinoma.

EXAMPLE 19

Transdermal skin patch

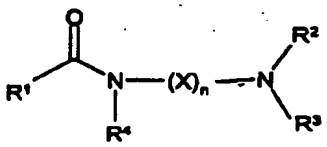
N-acetyl, N-(3-(N-ethyl-N-isobutyl)aminopropyl-3-amino-6-bromofluorene	450 mg
propylene glycol	10 mg
elastomer	5 mg
methyl cellulose	50 mg
sodium carboxymethyl cellulose	25 mg

The above ingredients are blended and spread onto an elastic tape. The tape is applied to the skin surface of a mammal to prevent and treat migraine pain.

The compounds of Formula I are useful for treating all conditions resulting from disorders within the central nervous system in animals, including humans. Commonly treated conditions include pain, depression, anxiety and schizophrenia. Other conditions that can be treated according to this invention include seizure disorders, i.e. epilepsy, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, migraine, cerebral ischemia, and compulsive disorders such as narcotic addiction, alcoholism, smoking addiction, appetite disorders such as bulimia and obesity, sexual performance, and sleeping disorders.

What is claimed is:

1. A compound of formula I



wherein :

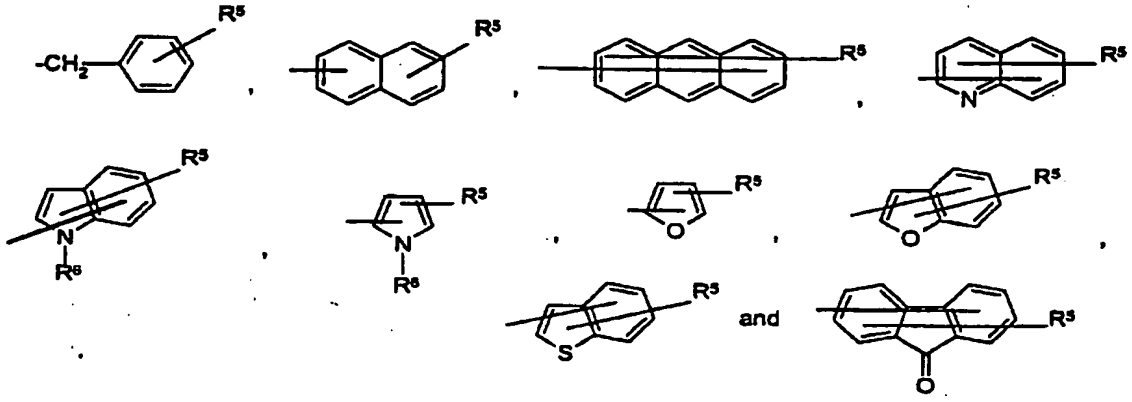
R^1 is hydrogen, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

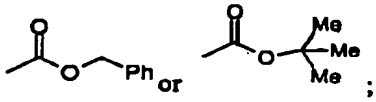
R^2 and R^3 independently are hydrogen, C_1-C_4 alkyl, phenyl or benzyl, or taken together with the nitrogen to which they are attached complete a ring having from 4 to 7 ring atoms, one optionally being oxygen;

X is $(CH_2)_n$, CHMe-$(CH_2)_{n-1}$ or $(CH_2)_{n-1}$-CHMe,

n is 1, 2 or 3;

R^4 is an aromatic or heteroaromatic group selected from



wherein R^5 is hydrogen, halogen, C_1-C_4 alkyl, nitro, N_3 or CF_3 and R^6 is hydrogen, C_{1-4} alkyl, -(C=O)Me, -(C=O)NH_2,  ;

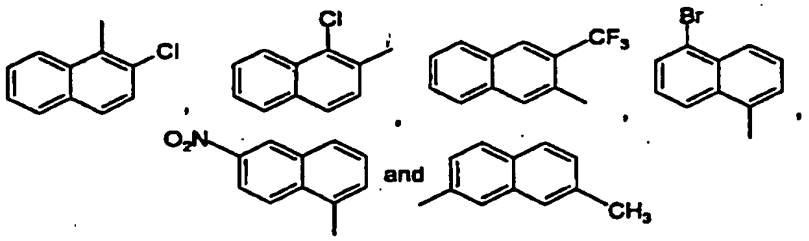
and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R^1 is C_1-C_4 alkyl.

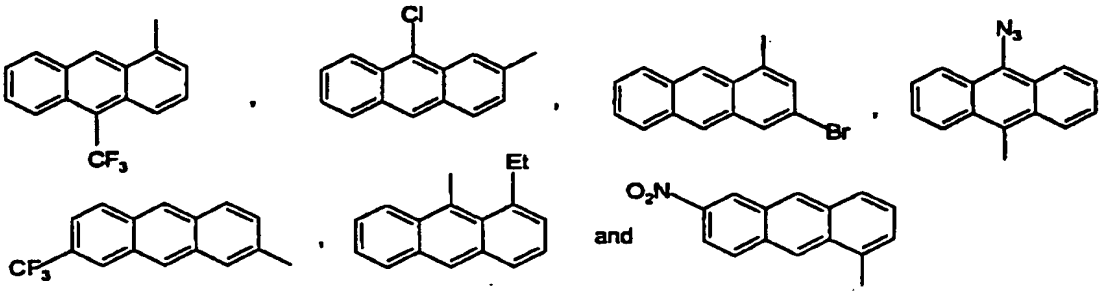
3. A compound according to Claim 2 wherein R^2 and R^3 independently are C_1-C_4 alkyl.

4. A compound according to Claim 3 wherein n is 2 or 3.

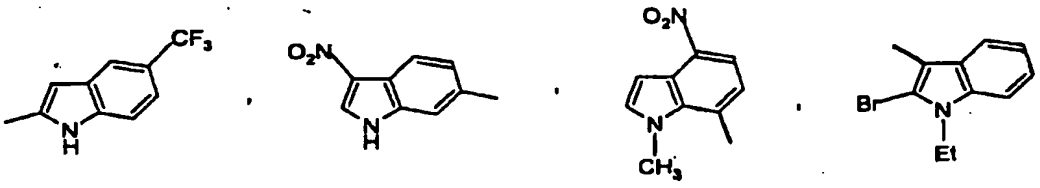
5. A compound according to Claim 4 wherein R^4 is selected from



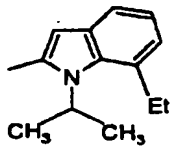
6. A compound according to Claim 4 wherein R^4 is selected from



7. A compound according to Claim 4 wherein R^4 is selected from

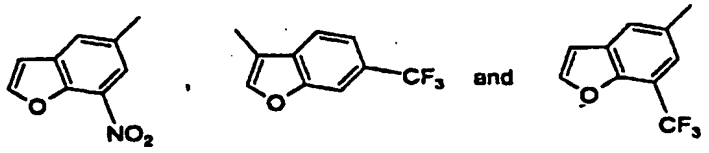


and

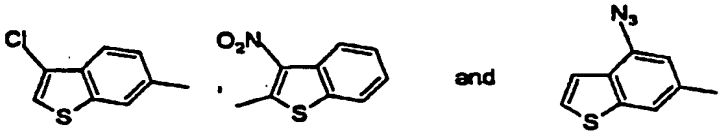


10

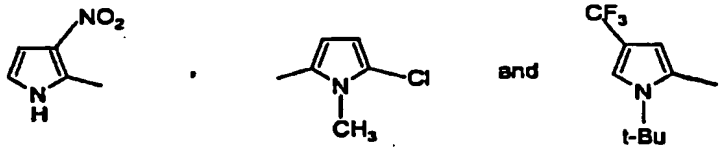
8. A compound according to Claim 4 wherein R^4 is selected from



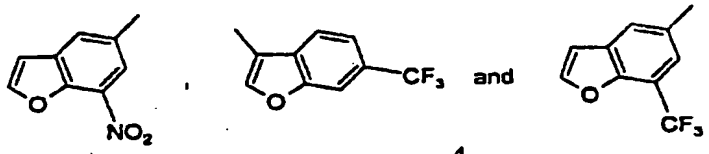
9. A compound according to Claim 4 wherein R^4 is selected from



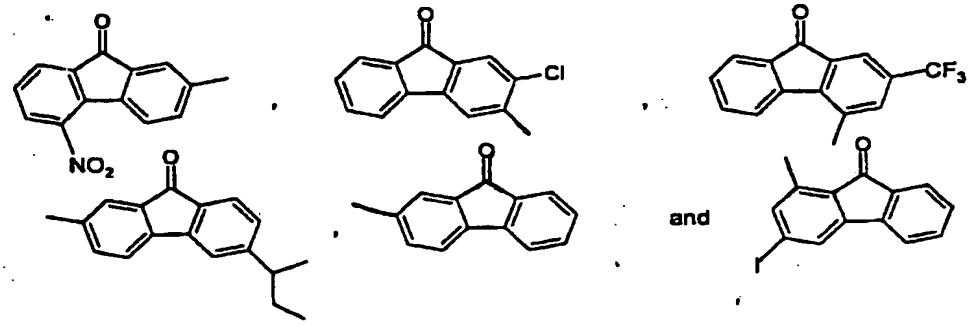
10. A compound according to Claim 4 wherein R^4 is selected from



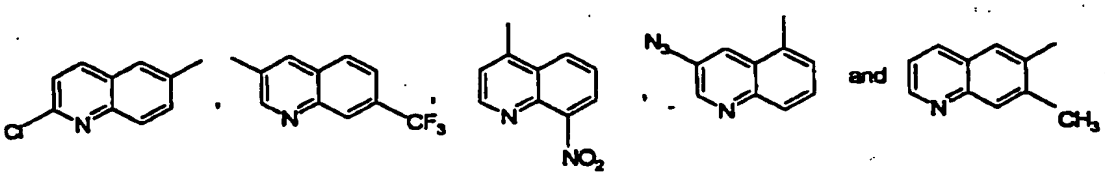
11. A compound according to Claim 4 wherein R^4 is selected from



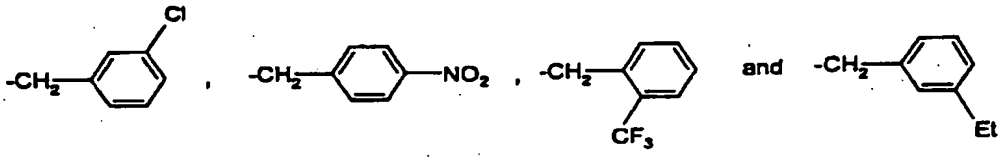
12. A compound according to Claim 4 wherein R^4 is selected from



13. A compound according to Claim 4 wherein R^4 is selected from



14. A compound according to Claim 4 wherein R^4 is selected from



15. A compound according to any one of Claims 5 to 14 which is selected from

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene
N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone
N-Propionyl, N-(2-Diethylaminoethyl)- 1-amino-4-bromonaphthalene
N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene
N-Propionyl, N-(2- (3-diethylamino-propyl))-1-amino-4-chloronaphthalene
N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene
N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzyl-amine
N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine
N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene
N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene
N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene
N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene
N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide
N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene, and
N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

16. N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene.

17. N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone.

18. N-Propionyl, N-(2-Diethylaminoethyl)- 1-amino-4-bromonaphthalene.

19. N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene.

20. N-Propionyl, N-(2- (3-diethylamino-propyl))-1-amino-4-chloronaphthalene.

21. N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene.

22. N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene.

23. N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

24. A compound according to any one of Claims 1 to 23 which is a pharmaceutically acceptable salt.

25. A pharmaceutical formulation comprising a compound of any one of Claims 1 to 24 together with a pharmaceutically acceptable diluent, carrier or excipient therefor.

26. A method for treating a CNS disorder in a mammal in need of treatment comprising administering a CNS effective amount of a compound of any one of Claims 1 to 24.

27. A method according to claim 26 wherein the CNS disorder is selected from pain, depression, anxiety, or schizophrenia.

28. A method according to Claim 26 wherein the CNS disorder is selected from Huntington's disease, Alzheimer's disease or amyotrophic lateral sclerosis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/36 C07D295/13 C07D215/46 A61K31/167 A61K31/445
A61K31/47 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EDWARD F. ELSLAGER ET AL.: "Respiratory Drugs. VIII. Ester and Amide Congeners of Amodiaquine, Hydroxychloroquine, Oxychloroquine, Primaquine, Quinacrine and Related Substances as Potential Long-Acting Antimalarial agents" JOURNAL OF MEDICINAL CHEMISTRY., vol. 12, no. 4, July 1969 (1969-07), pages 600-607, XP002145190 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 cited in the application page 603, column 1, 3rd paragraph and compound XIIIa	1-4
A	US 5 654 301 A (HAROLD L. KOHN ET AL.) 5 August 1997 (1997-08-05) claims; examples	1,25-28
	-/--	

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 13336 A (RESEARCH CORPORATION TECHNOLOGIES) 2 April 1998 (1998-04-02) claims; examples	1,25-28
A	WO 98 50343 A (SMITHKLINE BEECHAM) 12 November 1998 (1998-11-12) claims; examples	1,25-28

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5654301 A	05-08-1997	US 5378729 A	03-01-1995
		AU 657985 B	30-03-1995
		DE 69223965 D	12-02-1998
		DE 69223965 T	30-04-1998
		EP 0592490 A	20-04-1994
		JP 6510985 T	08-12-1994
		AT 161824 T	15-01-1998
		AU 2162192 A	08-01-1993
		CA 2110693 A	10-12-1992
		WO 9221648 A	10-12-1992
		AU 641160 B	16-09-1993
		AU 5519590 A	28-02-1991
		CA 2017217 A	19-11-1990
		EP 0400440 A	05-12-1990
		JP 3506045 T	26-12-1991
		NZ 233728 A	28-04-1993
		PT 94103 A,B	08-01-1991
		WO 9015069 A	13-12-1990
		AT 92315 T	15-08-1993
		DE 3786865 A	09-09-1993
		DE 3786865 T	09-12-1993
		DK 526087 A	08-04-1988
		EP 0263506 A	13-04-1988
		ES 2005042 A	16-02-1989
		ES 2058085 T	01-11-1994
		GR 871549 A	12-02-1988
		IE 61437 B	02-11-1994
		JP 2580196 B	12-02-1997
		JP 63132832 A	04-06-1988
		NZ 222045 A	27-10-1989
		PT 85869 A,B	01-11-1987
		AT 62222 T	15-04-1991
		AU 596573 B	10-05-1990
		AU 5371186 A	21-08-1986
		DE 3678469 D	08-05-1991
		DK 72686 A	16-08-1986
		EP 0194464 A	17-09-1986
		ES 552348 D	16-10-1987
		ES 8708142 A	01-12-1987
		GR 860455 A	18-06-1986
		IE 58422 B	22-09-1993
		JP 1972065 C	27-09-1995
		JP 6104649 B	21-12-1994
		JP 61200950 A	05-09-1986
		PT 82032 A,B	01-03-1986
WO 9813336 A	02-04-1998	US 5880158 A	09-03-1999
WO 9850343 A	12-11-1998	NONE	

[redacted]

Express Mail No. ET401306226US

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/36 C07D295/13 C07D215/46 A61K31/167 A61K31/445
A61K31/47 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EDWARD F. ELSLAGER ET AL.: "Respiratory Drugs. VIII. Ester and Amide Congeners of Amodiaquine, Hydroxychloroquine, Oxychloroquine, Primaquine, Quinacrine and Related Substances as Potential Long-Acting Antimalarial agents" JOURNAL OF MEDICINAL CHEMISTRY., vol. 12, no. 4, July 1969 (1969-07), pages 600-607, XP002145190 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 cited in the application page 603, column 1, 3rd paragraph and compound XIIIa	1-4
A	US 5 654 301 A (HAROLD L. KOHN ET AL.) 5 August 1997 (1997-08-05) claims; examples	1,25-28

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 13336 A (RESEARCH CORPORATION TECHNOLOGIES) 2 April 1998 (1998-04-02) claims; examples	1,25-28
A	WO 98 50343 A (SMITHKLINE BEECHAM) 12 November 1998 (1998-11-12) claims; examples	1,25-28

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5654301 A	05-08-1997	US 5378729 A	03-01-1995
		AU 657985 B	30-03-1995
		DE 69223965 D	12-02-1998
		DE 69223965 T	30-04-1998
		EP 0592490 A	20-04-1994
		JP 6510985 T	08-12-1994
		AT 161824 T	15-01-1998
		AU 2162192 A	08-01-1993
		CA 2110693 A	10-12-1992
		WO 9221648 A	10-12-1992
		AU 641160 B	16-09-1993
		AU 5519590 A	28-02-1991
		CA 2017217 A	19-11-1990
		EP 0400440 A	05-12-1990
		JP 3506045 T	26-12-1991
		NZ 233728 A	28-04-1993
		PT 94103 A,B	08-01-1991
		WO 9015069 A	13-12-1990
		AT 92315 T	15-08-1993
		DE 3786865 A	09-09-1993
		DE 3786865 T	09-12-1993
		DK 526087 A	08-04-1988
		EP 0263506 A	13-04-1988
		ES 2005042 A	16-02-1989
		ES 2058085 T	01-11-1994
		GR 871549 A	12-02-1988
		IE 61437 B	02-11-1994
		JP 2580196 B	12-02-1997
		JP 63132832 A	04-06-1988
		NZ 222045 A	27-10-1989
		PT 85869 A,B	01-11-1987
		AT 62222 T	15-04-1991
		AU 596573 B	10-05-1990
		AU 5371186 A	21-08-1986
		DE 3678469 D	08-05-1991
		DK 72686 A	16-08-1986
		EP 0194464 A	17-09-1986
		ES 552348 D	16-10-1987
		ES 8708142 A	01-12-1987
		GR 860455 A	18-06-1986
		IE 58422 B	22-09-1993
		JP 1972065 C	27-09-1995
		JP 6104649 B	21-12-1994
		JP 61200950 A	05-09-1986
		PT 82032 A,B	01-03-1986
WO 9813336 A	02-04-1998	US 5880158 A	09-03-1999
WO 9850343 A	12-11-1998	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PFIM/P22403PC		

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB00/01788	10/05/2000	10/05/1999

International Patent Classification (IPC) or national classification and IPC
C07C233/36

Applicant
WARNER-LAMBERT COMPANY et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority.
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/11/2000	07.08.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Slootweg, A

Telephone No. +49 89 2399 8328

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01788

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, pages:

1-21 as originally filed

Claims, No.:

1-29 as received on 15/06/2001 with letter of 14/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01788

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 27-29.

because:

☒ the said international application, or the said claims Nos. See Separate Sheet. relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01788

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB00/01788

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. For the assessment of the present claims 26-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. Claims 26-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:

D1	=	EDWARD F. ELSLAGER ET AL.: 'Repository Drugs. VIII., J. Med. Chem., vol. 12, no. 4, July 1969 (1969-07), pages 600-607, cited in the application,
D2	=	US-A-3 118 941,
D3	=	LARIZZA, ANGELO ET AL.: Gazz. Chim. Ital., vol 90, 1960, p. 848- 862,
D4	=	MÖHRLE ET AL.: Arch. Pharm., no. 316, 1983, p.251-256,
D5	=	MÖHRLE ET AL.: Arch. Pharm., no. 303, 1970, p.531-544,
D6	=	MÖHRLE ET AL.: Arch. Pharm., no.316, 1983, P. 222-229,
D7	=	SCHWARTZ ET AL.: Tett. Lett., vol. 23, no. 9, 1982, p. 979-82,
D8	=	MÖHRLE ET AL.: Tetrahedron, vol 26,, 1970, p. 4895-4900,
D9	=	Compound with CAS reg. nr 92493-02-2 (Beilstein extract)
D10	=	WO-A-98/50343

D11 = WO-A-98/13336
D12 = US-A-5 654 301

The documents D2-D9 were not cited in the international search report. Copies of the documents are appended hereto.

3. The document D1 discloses on p.603 the compounds XIIIa and XIIIb stating that this is useful as an antimalarial repository drug.

4. The document D3 discloses at the bottom of p. 849 the compound Ph-CH_2-NR-CHR_1CH_2-R_2 with definitions given for R, R_1 and R_2 (compounds are defines as being anti-histaminic). See also the compounds in Table II on p. 852 the compounds 201 FC and 198 FC.

5. Documents D2, D4-D9 also disclose compounds which have been disclaimed from claim 1 but no medical use is indicated for any of the compounds disclosed. The medical use claim is therefore formulated to include these compounds.

6. The closest prior art documents are considered to be the documents D10-D12 which disclose different amide compounds for use in the treatment of CNS disorders (D10), specifically as anti convulsant (D11-D12).

7. The problem to be solved by the present application can be see to provide alternative compounds which can be used in the treatment of CNS disorders.

8. The solution to this problem is the compounds as claimed in claim 1 (the compounds which were disclosed in D1-D9 have been excluded by means of a disclaimer). As such claim 1 can be considered to satisfy Art. 33 (2) PCT, with respect to the cited prior art.

9. There is no indication in the prior art documents which could have led the skilled man to make such compounds to treat CNS disorders. The documents D1 and D3 do show a medical use but not the use to treat CNS disorders. Claim 1 can, therefore, also be considered to satisfy Art. 33 (3) PCT, with respect to the cited prior art.

10. Claims 2-24 are dependent on claim 1 and as such can also be considered to satisfy Art. 33 (2) and (3) PCT for the same reasons.

11. Claim 25 is a claim towards pharmaceutical compositions of compounds according to claim 1 including the compounds disclosed in D2, and D4-D9 (which did not exhibit any medical use), but excluding the compounds disclosed in D1 and D3 (which did exhibit a medical use). Claim 26 is a claim towards the medical use of the compounds defined in claim 25. Claims 25 and 26 can, therefore, also be considered to satisfy Art. 33 (2) and (3) PCT, with respect to the cited prior art.

Re Item VII

Certain defects in the international application

12. The citation given on p. 1, l. 26-28 of the description obviously contains an error since this document could not be retrieved.

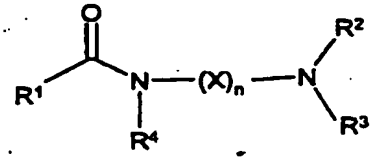
13. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D12 is not mentioned in the description, nor are these documents identified therein.

10/019993

23531 Rec'd PC 09 NOV 2001

What is claimed is:

1. A compound of formula I



wherein :

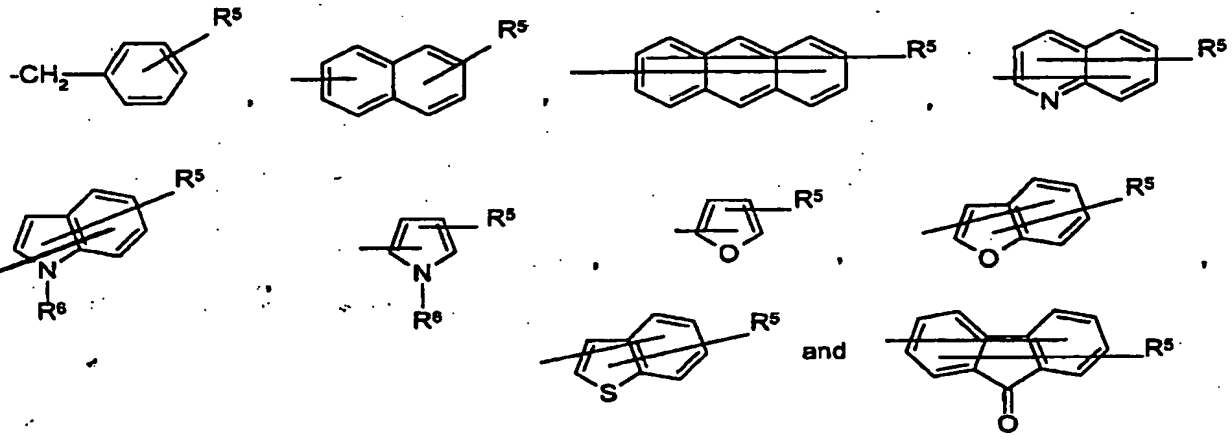
R^1 is hydrogen, C_1-C_4 alkyl, or C_2-C_4 alkenyl;

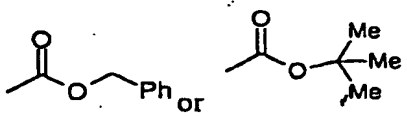
R^2 and R^3 independently are hydrogen, C_1-C_4 alkyl, phenyl or benzyl, or taken together with the nitrogen to which they are attached complete a ring having from 4 to 7 ring atoms, one optionally being oxygen;

X is $(CH_2)_n$, $CHMe\text{-}(CH_2)_{n-1}$ or $(CH_2)_{n-1}\text{-}CHMe$,

n is 1, 2 or 3;

R^4 is an aromatic or heteroaromatic group selected from



wherein R^5 is hydrogen, halogen, C_1-C_4 alkyl, nitro, N_3 or CF_3 and R^6 is hydrogen, C_{1-4} alkyl, -(C=O)Me, -(C=O)NH_2,  or ;

and the pharmaceutically acceptable salts thereof

with the proviso that in formula I:

when R^1 is CH_3, $(X)_n$ is $(CH_2)_3$, and R^2 and R^3 are both ethyl, R^4 is not 7-chloroisoquinol-4-yl;

when R^1 is H, $(X)_n$ is $(CH_2)_2$ and R^2 and R^3 are both ethyl, R^4 is not benzyl, 4-methylbenzyl, 4-chlorobenzyl, 2-chlorobenzyl, 4-bromobenzyl, 3-ethylbenzyl, 4-isopropylbenzyl, 4-n-propylbenzyl, 3-n-butylbenzyl, 2-t-butylbenzyl, 4-s-butylbenzyl or 2-bromobenzyl;

when R^1 is methyl or ethyl, $(X)_n$ is $CHMeCH_2$ and NR^2R^3 is N-piperidinyl, R^4 is not benzyl;

when R^1 is H, $(X)_n$ is CH_2 and R^4 is benzyl, NR^2R^3 is not $NHCH_2Ph$, N-piperidinyl, NH-t-butyl, N-morpholinyl, N-pyrrolidinyl, N-azepinyl, $N(CH_3)_2$ or $N(CH_2CH_3)_2$; and

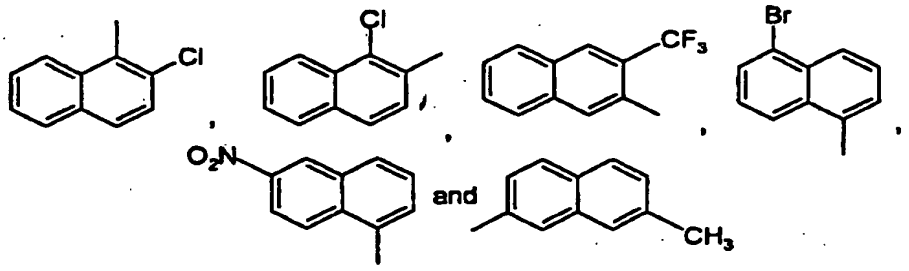
when R^1 is n-butyl, $(X)_n$ is $(CH_2)_2$ and R^4 is benzyl, NR^2R^3 is not $NHCH_2Ph$

2. A compound according to claim 1 wherein R^1 is C_1-C_4 alkyl.

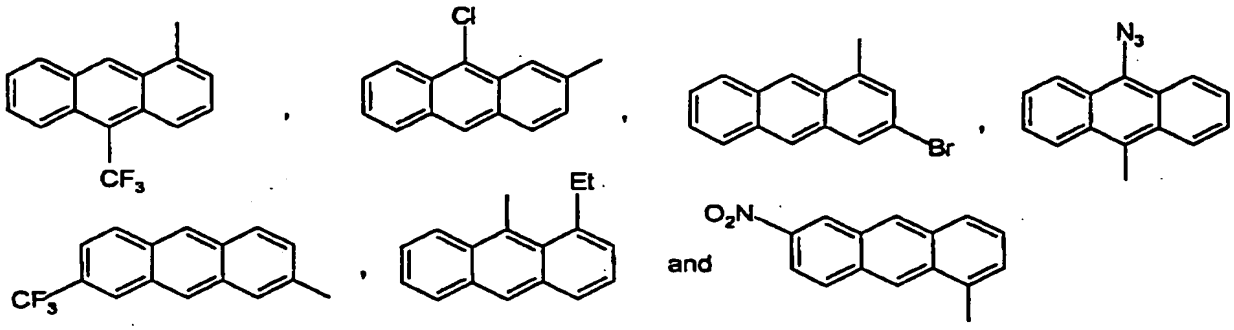
3. A compound according to Claim 2 wherein R^2 and R^3 independently are C_1-C_4 alkyl.

4. A compound according to Claim 3 wherein n is 2 or 3.

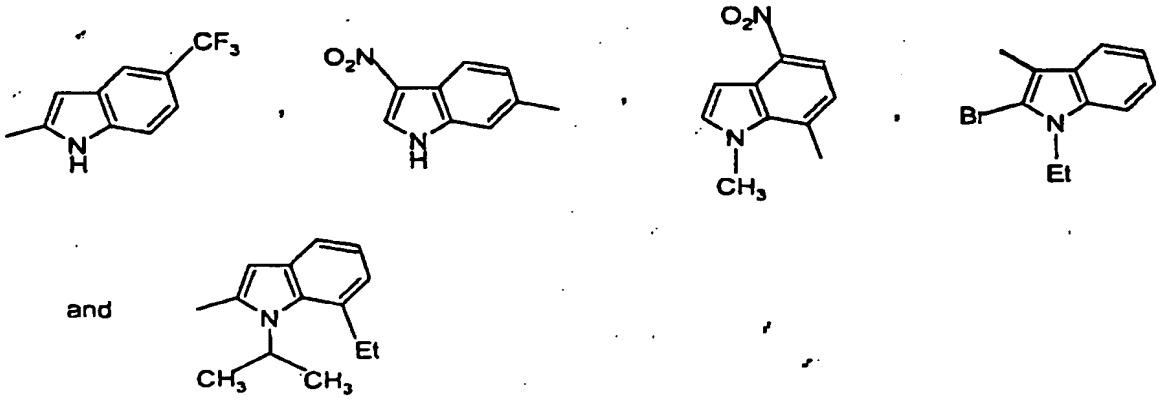
5. A compound according to Claim 4 wherein R^4 is selected from



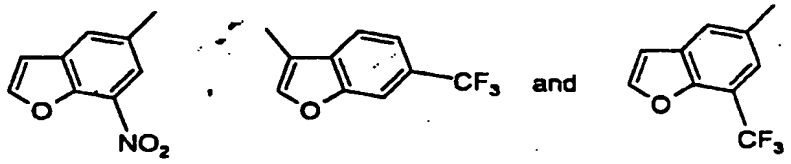
6. A compound according to Claim 4 wherein R^4 is selected from



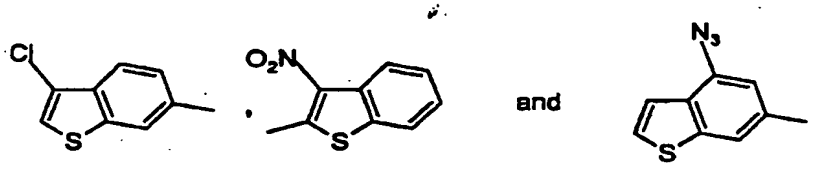
7. A compound according to Claim 4 wherein R^4 is selected from



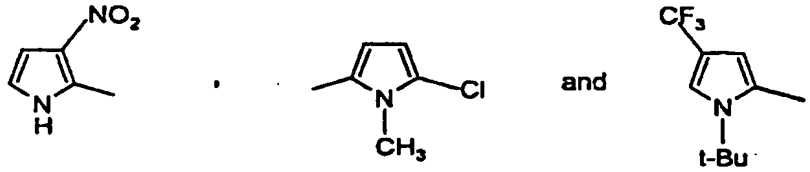
8. A compound according to Claim 4 wherein R^4 is selected from



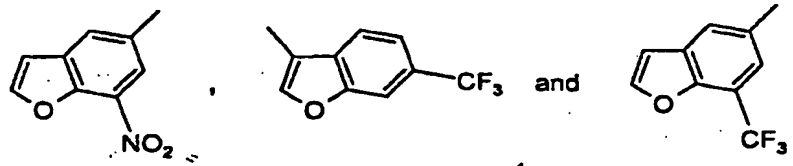
9. A compound according to Claim 4 wherein R^4 is selected from



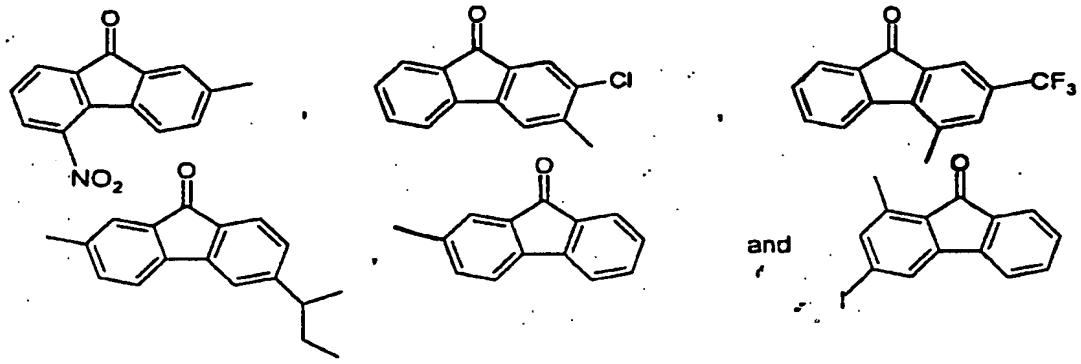
10. A compound according to Claim 4 wherein R^4 is selected from



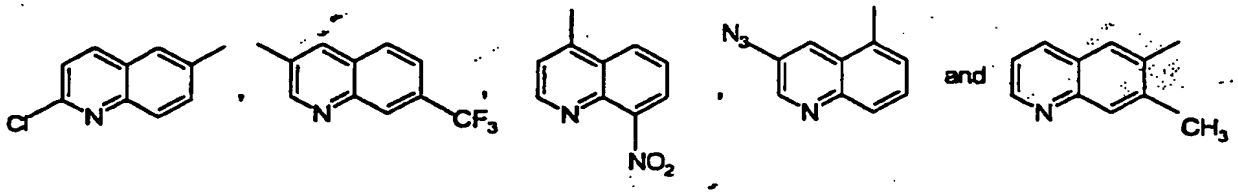
11. A compound according to Claim 4 wherein R^4 is selected from



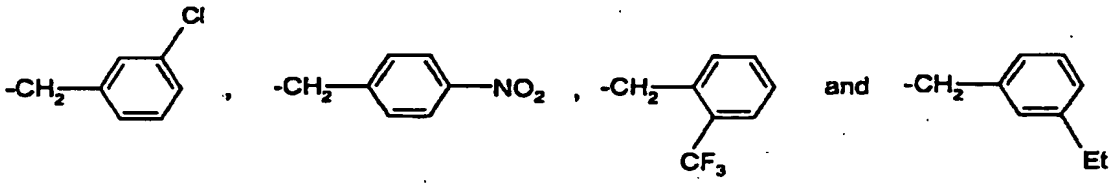
12. A compound according to Claim 4 wherein R^4 is selected from



13. A compound according to Claim 4 wherein R^4 is selected from



14. A compound according to Claim 4 wherein R^4 is selected from



15. A compound according to any one of Claims 5 to 14 which is selected from

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone

N-Propionyl, N-(2-Diethylaminoethyl)- 1-amino-4-bromonaphthalene

N-Propionyl, N-(N-Morpholino)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2- (3-diethylamino-propyl))-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-azidonaphthalene

N-Propionyl, N-(2-Diethylaminoethyl)-3-chlorobenzyl-amine

N-Propionyl, N-(2-Diethylaminoethyl)-3-bromobenzyl-amine

N-Propionyl, N-(2-Piperidylethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-(3-dimethylamino-propyl))-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-Dimethylaminoethyl)-1-amino-4-chloronaphthalene

N-Propionyl, N-(2-(N-benzyl)-aminoethyl)-1-aminonaphthalene

N-(2-Diethylamino-ethyl)-*N*-(7-methyl-quinolin-4-yl)-propionamide

N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene, and

N-Propionyl, N-(2-Diethylaminoethyl)-(1-amino-4-nitronaphthalene).

16. N-Propionyl, N-(2-Diethylaminoethyl)-1-amino-4-chloronaphthalene.

17. N-Propionyl, N-(2-Diethylaminoethyl)-4-amino-9-fluorenone.

18. N-Propionyl, N-(2-diethylaminoethyl)- 1-amino-4-bromonaphthalene.

19. N-Propionyl, N-(N-morpholino)-1-amino-4-chloronaphthalene.

20. N-Propionyl, N-(2-(3-diethylamino-propyl))-1-amino-4-chloronaphthalene.

21. N-Propionyl, N-(2-diethylaminoethyl)-1-amino-4-azidonaphthalene.

22. N-Acryloyl, N-(2-diethylaminoethyl)-1-amino-4-chloronaphthalene.

23. N-Propionyl, N-(2-diethylaminoethyl)-(1-amino-4-nitronaphthalene).

24. A compound according to any one of Claims 1 to 23 which is a pharmaceutically acceptable salt.

25. A pharmaceutical formulation comprising a compound of any one of Claims 1 to 24 as defined in formula I without the proviso in Claim 1, provided that:
when R^1 is CH_3, $(X)_n$ is $(CH_2)_3$ and R^2 and R^3 are both ethyl, R^4 is not 7-chloroisoquinol-4-yl; and
when R^1 is methyl or ethyl, $(X)_n$ is $CHMeCH_2$ and NR^2R^3 is N-piperidinyl, R^4 is not benzyl.

26. Compound as defined in Claim 25 for use in medicine.

27. A method for treating a CNS disorder in a mammal in need of treatment comprising administering a CNS effective amount of

compound of formula I as defined in any one of Claims 1 to 24 without the proviso in Claim 1.

28. A method according to Claim 27 wherein the CNS disorder is selected from pain, depression, anxiety, or schizophrenia.

29. A method according to Claim 27 wherein the CNS disorder is selected from Huntington's disease, Alzheimer's disease or amyotrophic lateral sclerosis.